Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

# General

## Guideline Title

Cystic Fibrosis Foundation pulmonary guideline. Pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection.

## Bibliographic Source(s)

Mogayzel PJ, Naureckas ET, Robinson KA, Brady C, Guill M, Lahiri T, Lubsch L, Matsui J, Oermann CM, Ratjen F, Rosenfeld M, Simon RH, Hazle L, Sabadosa K, Marshall BC, Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Foundation pulmonary guideline. Pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. Ann Am Thorac Soc. 2014 Dec;11(10):1640-50. [46 references] PubMed

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Recommendations

## Major Recommendations

Definitions of the grade of recommendation (A, B, C, D, I), and the certainty of net benefit (High, Moderate, Low) are provided at the end of the "Major Recommendations" field.

1. The Cystic Fibrosis (CF) Foundation strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *Pseudomonas aeruginosa* (*P. aeruginosa*) from an airway culture (certainty of net benefit, high; estimate of net benefit, substantial; grade of recommendation, A). The favored antibiotic regimen is inhaled tobramycin (300 mg twice daily) for 28 days.
2. The CF Foundation recommends against the use of prophylactic antipseudomonal antibiotics to prevent the acquisition *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, zero; grade of recommendation, D).
3. The CF Foundation recommends routine oropharyngeal cultures rather than bronchoalveolar lavage cultures obtained by bronchoscopy in individuals with CF who cannot expectorate sputum to determine if they are infected with *P. aeruginosa* (certainty of net benefit, moderate; estimate of net benefit, moderate; grade of recommendation, B).

Definitions

U.S. Preventive Services Task Force (USPSTF) Evidence Grading*

| Certainty of Net Benefit | Magnitude of Net Benefit (Benefit minus Harms) | | | |
|---|---|---|---|---|
| | Substantial | Moderate | Small | Zero/Negative |
| High | A | B | C | D |
| Moderate | B | B | C | D |
| Low | I (insufficient evidence) | | | |

*The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm.

*Certainty of Net Benefit*

High = The available evidence includes consistent results from well designed, well-conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

Moderate = The available evidence is sufficient to determine the effects of the therapy on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings; or a lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low = The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of a limited number or size of studies, important flaws in study design or methods, inconsistency of findings across individual studies, gaps in the chain of evidence; findings not generalizable, or lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Strength of Recommendation

A = The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

B = The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

C = The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms, there is likely to be only a small benefit from this therapy.

D = The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this therapy.

I = The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the therapy. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

- *Pseudomonas aeruginosa* (*P. aeruginosa*) infection
- Cystic fibrosis (CF)

## Guideline Category

Management

Prevention

Treatment

## Clinical Specialty

Infectious Diseases

Pediatrics

Preventive Medicine

Pulmonary Medicine

## Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

## Guideline Objective(s)

To develop clinical care guidelines for:

- The prevention of *Pseudomonas aeruginosa* (*P. aeruginosa*) infection
- The initial treatment of *P. aeruginosa* infection
- The use of bronchoscopy to obtain routine airway cultures in individuals with cystic fibrosis (CF)

## Target Population

Individuals with cystic fibrosis (CF)

## Interventions and Practices Considered

1. Inhaled antibiotic therapy (tobramycin)
2. Prophylactic antipseudomonal antibiotics (not recommended)
3. Routine oropharyngeal cultures

## Major Outcomes Considered

Cultures without growth of *Pseudomonas aeruginosa* (*P. aeruginosa*)

# Methodology

## Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Systematic reviews were commissioned from The Johns Hopkins University. Searches of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were conducted and completed in May 2012 and updated in August 2013. All relevant articles were included, and the search was not limited by date. The searches combined controlled vocabulary terms and text words for cystic fibrosis (CF) and terms relevant for each question to create comprehensive search strategies (see the online supplement [see the "Availability of Companion Documents" field]). Reference lists of relevant Cochrane reviews were also scanned, and references of eligible articles were examined. All identified citations were imported into a database maintained in reference management software (ProCite; ThomsonReuters, New York, NY). A custom workform was used to track the search results. Citations were uploaded into a Web-based system (DistillerSR; Evidence Partners Inc., Ottawa, ON, Canada) to complete and track the screening process. Two reviewers independently screened citations for eligibility, first using title and abstract. Citations determined to be potentially eligible were subsequently screened using the full text or full article. Predefined eligibility criteria were applied during the screening process. However, additional criteria were added for the full-text screen based on feedback from the chairs of the committee to remove studies of individuals with chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) infection. Specifically, studies with a population defined by authors as chronically infected with *P. aeruginosa* or articles stating that subjects had two or more positive *P. aeruginosa* cultures in previous 12 months were excluded from consideration. Disagreements concerning eligibility were resolved by consensus or by a third reviewer.

The search identified 3,547 unique citations, of which 18 citations describing 13 studies were eligible for inclusion (see Figure 1 in the original guideline document). The reviewers identified seven treatment trials of initial or newly acquired *P. aeruginosa* infection that ranged in size from 21 to 304 individuals with CF. Only three of the seven trials concealed allocation of study subjects to the intervention and used blinded or masked outcome assessment. Two trials compared inhaled tobramycin with placebo. One trial compared inhaled colistin and oral ciprofloxacin with no therapy. Four studies compared a variety of combinations of oral ciprofloxacin, inhaled colistin, and inhaled tobramycin for treatment of *P. aeruginosa* infection. Two studies evaluated antibiotic or vaccine prophylaxis to prevent infection. Four studies evaluated the accuracy of oropharyngeal (OP) cultures compared with bronchoalveolar lavage fluid (BALF) cultures for the identifying *P. aeruginosa* infection.

## Number of Source Documents

18 articles (describing 13 studies) were included. See Figure 1 in the original guideline document for a flow diagram of the literature search.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

U.S. Preventive Services Task Force (USPSTF) Evidence Grading*

| Certainty of Net Benefit | Magnitude of Net Benefit (Benefit minus Harms) | | | |
|---|---|---|---|---|
| | Substantial | Moderate | Small | Zero/Negative |
| High | A | B | C | D |
| Moderate | B | B | C | D |
| Low | I (insufficient evidence) | | | |

*The overall strength of the evidence is based on the certainty of the magnitude of benefit defined as benefit minus harm.

Certainty of Net Benefit

High = The available evidence includes consistent results from well designed, well-conducted studies in representative populations. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

Moderate = The available evidence is sufficient to determine the effects of the therapy on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings; or a lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low = The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of a limited number or size of studies, important flaws in study design or methods, inconsistency of findings across individual studies, gaps in the chain of evidence; findings not generalizable, or lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

## Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Data abstraction forms were developed based on the forms from prior projects. Using the forms, two reviewers abstracted information about study and participant characteristics and about outcomes from each eligible article. Information from completed forms was entered into a custom designed database (Access; Microsoft, Redmond, WA). Evidence tables were created from the database and provided to the committee members as Excel spreadsheets (Microsoft).

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

An 18-member multidisciplinary committee developed a series of questions about the effectiveness of prevention and eradication strategies for *Pseudomonas aeruginosa* (*P. aeruginosa*) infection and the use of bronchoscopy to obtain routine airway cultures. The outcome of interest was cultures without growth of *P. aeruginosa*. The key questions were as follows. (1) What is the best eradication therapy for a newly acquired *P. aeruginosa* infection? (2) Can prophylactic antibiotic therapy prevent *P. aeruginosa* infection? (3) What is the role of bronchoscopy in obtaining routine airway cultures?

The committee met in October 2012 and October 2013 to review the evidence and to make recommendations. Committee members disclosed any potential conï¬‚icts of interest in writing to the Cystic Fibrosis (CF) Foundation. One member, having previously served on an advisory board, was recused from discussion of inhaled aztreonam. Three committee members served as principal investigators for studies reviewed by the committee. These individuals recused themselves from discussion of these studies, but they did participate in the formulation of the recommendations.

The evidence was reviewed by the committee, and the final recommendations were graded using the U.S. Preventive Services Task Force (USPSTF) system, which assesses net benefit and certainty of net benefit (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields). The domains considered by the committee to determine the certainty of benefit included the number of trials identified by the search, the number of participants in each trial, the consistency of findings between the trials, and the likelihood that future studies would alter the recommendation of the committee. In addition, the committee members were provided with a report that included risk of bias assessments based on the Cochrane risk of bias tool.

## Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

A = The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.

B = The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

C = The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms, there is likely to be only a small benefit from this therapy.

D = The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this therapy.

I = The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the therapy. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

### Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

### Method of Guideline Validation

Internal Peer Review

### Description of Method of Guideline Validation

A draft manuscript with recommendations was posted on the Cystic Fibrosis (CF) Foundation intranet for review and comment by members of the CF professional community and patient and parent representatives. These comments were considered in the final preparation of the guidelines.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Preventing chronic infection with *Pseudomonas aeruginosa* (*P. aeruginosa*) has the potential to improve the lives of individuals with cystic fibrosis (CF). Unfortunately, the committee was not able to identify an effective strategy to prevent initial *P. aeruginosa* infection. However, the recommendation of 28 days of inhaled tobramycin for the treatment of newly acquired *P. aeruginosa* is likely to be effective in infected individuals.

### Potential Harms

- Potential medication side effects
- Potential false-positive and false-negative results of oropharyngeal cultures

## Qualifying Statements

## Qualifying Statements

These guidelines were developed and supported by the Cystic Fibrosis (CF) Foundation and are not official guidelines from the American Thoracic Society (ATS). They have not been reviewed or endorsed by the ATS Board of Directors.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

## Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

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## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2014 Dec

## Guideline Developer(s)

Cystic Fibrosis Foundation - Disease Specific Society

## Source(s) of Funding

These guidelines were developed and supported by the Cystic Fibrosis (CF) Foundation.

## Guideline Committee

Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

Committee members disclosed any potential conï¬‚icts of interest in writing to the Cystic Fibrosis (CF) Foundation. One member, having previously served on an advisory board, was recused from discussion of inhaled aztreonam. Three committee members served as principal investigators for studies reviewed by the committee. These individuals recused themselves from discussion of these studies, but they did participate in the formulation of the recommendations.

Author disclosures are available at the American Thoracic Society (ATS) Journals Web site .

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the Annals of the American Thoracic Society Web site .

## Availability of Companion Documents

The following is available:

- Mogayzel PJ. Naureckas ET, Robinson KA, Brady C, Guil Ml, Lahiri T, Lubsch L, Matsui J, Oermann CM, Ratjen F, Rosenfeld M, Simon RH, Hazle L, Sábados K, Marshall B, Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. Online supplement. 2014. 4 p. Available from the Annals of the American Thoracic Society Web site .

## Patient Resources

The following is available:

- Pseudomonas. Patient information. Bethesda (MD): Cystic Fibrosis Foundation. Available from the Cystic Fibrosis Foundation Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

This NGC summary was completed by ECRI Institute on March 22, 2016. The information was verified by the guideline developer on May 25, 2016.

## Copyright Statement



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